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Michael Roger Cane et al.

Application No. 09/760,387

Confirmation No. 2484

Filed: January 12, 2001

Examiner: Ruth S. Smith

"METHOD OF AND APPARATUS FOR INVESTIGATING TISSUE HISTOLOGY"

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Sir:

Enclosed are the priority documents for British Patent Application 9624003.1, 9912908.2 and 9925414.6, filed November 19, 1996, June 4, 1999 and October 28, 1999 from which the above-identified U. S. patent application claims priority. Please charge the $130.00 fee for submitting the priority documents after payment of the issue fee specified in 37 CFR 1.17(i) to deposit account number 13-3080. Please charge any other fees due or credit any overpayment to deposit account number 13-3080.

Respectfully submitted,

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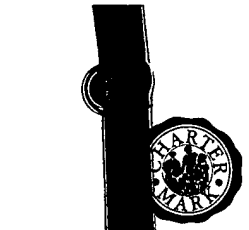

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2. Patent application number *(The Patent Office will fill in this part)* — 9624003.1 — 19 NOV 1996

3. Full name, address and [illegible] each applicant *(underline)*

The University of Birmingham
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If the applicant is a corporate body, give the country/state of its incorporation — England — 7981650002

4. Title of the invention — METHOD AND APPARATUS FOR MEASUREMENT OF SKIN HISTOLOGY

5. Name of your agent *(if you have one)* — Marks & Clerk

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METHOD AND APPARATUS FOR MEASUREMENT OF SKIN HISTOLOGY

This invention relates to a method and apparatus for the non-invasive measurement of skin histology and is particularly, but not exclusively, concerned with a method and apparatus for identifying and measuring the depth of dermal invasion of melanocytes. The extent of dermal invasion within a skin cancer is considered to be the most important factor governing a patient's prognosis. The present invention is considered to be potentially useful for the preliminary screening of patients to identify those who should be referred to an appropriate clinician for diagnosis and further to assist the clinician in diagnosis.

The present invention is based on the findings reported by Symon D'O Cotton in "Do all human skin colours lie on a defined surface within LMS space?", University of Birmingham Technical Report, 30 December 1995. The disclosure of such Technical Report is included herein by reference. In this Technical Report, the relation between healthy skin and the colour of the skin represented in LMS, a particular colour space, is reported, and it discloses that, for healthy skin, the colouration, regardless of race or amount of tanning, lies on a defined curved surface within a three-dimensional colour space. This, if used with a correct colour measurement system, can measure and quantify the amount of melanin and blood at any particular point at which this measurement is made. If the skin is sampled as an image, then corresponding images showing the variation of blood and melanin across the skin can be obtained. In the above Technical Report, it is disclosed that melanocytes can sometimes penetrate into the dermis producing the characteristic blue hues of blue

nevi and melanoma and that this melanocytic descent has been quantified by Clark et al ("The Histogenesis and Biological Behaviour of Primary Human Malignant Melanomas of the Skin", Cancer Research, 29, 1989) into five levels of tumour invasion, in which level 1 corresponds to invasion into the epidermis, level 2 corresponds to invasion into the papillary dermis, etc. In an alternative system, the extent of tumour invasion in mm from the cornified layer is expressed as the Breslow thickness. The above Technical Report also acknowledges that, in the case of melanoma, CD Neville ("Melanoma: Issues of Importance to the Clinician", British Journal of Hospital Medicine, March 1985) discloses the existence of a strong relationship between this level of invasion and prognosis. However, the above Technical Report does not disclose in detail any method or apparatus suitable for taking the necessary measurements.

According to one aspect of the present invention, there is provided a method of non-invasively analysing skin structure, comprising the steps of:
(i) measuring infrared radiation from a plurality of locations over an area of skin under investigation so as to give an indication of the variation in papillary dermis thickness over said area;
(ii) measuring the skin colour coordinates at a plurality of locations over said area of skin;
(iii) using data obtained in measuring steps (i) and (ii) to calculate corrected skin colour coordinates over said area which corresponds to a predetermined papillary dermis thickness, and;
(iv) comparing the corrected skin colour coordinates obtained in step (iii) with a reference colour coordinate range for healthy skin of the same predetermined papillary dermis thickness.

The method can be used for locating and measuring the properties of a skin abnormality, in which case the method further comprises the steps of;

(v) identifying an abnormal location within said area of skin where the corrected skin colour coordinates lie outside the reference colour coordinate range;

(vi) calibrating the corrected skin colour coordinates of said abnormal location with the corrected skin colour coordinates of at least one adjacent skin location having colour coordinates lying within said reference colour coordinate range for healthy skin, and;

(vii) using the skin colour coordinates to assess the degree of abnormality of said abnormal skin location.

It is to be understood that using this method, it is possible to reconstruct a full 3D model of the skin architecture which conveys information grossly comparable to that available through microscopical examination of biopsied skin tissue.

It has been found that the papillary dermal skin thickness can change markedly with some skin lesions which are not otherwise of concern. This throws the colouration of the skin off the surface of predicted colouration and so can give rise to false positives during measurement of skin histology containing skin lesions. It is for this reason that papillary dermis thickness is measured first, and subsequent calculations are based on the skin colour coordinates corrected to a predetermined papillary dermis thickness. Any arbitrary value for this thickness may be chosen, such as 2.0×10^{-4} m which is the average value for healthy human skin.

The thickness of the papillary dermis may be obtained by utilising the property of human skin to vary its absorption of infrared radiation with varying papillary dermis thickness. In general, there is an inverse relationship between absorption and thickness. The fact that infrared radiation is also absorbed by other materials within the skin, particularly melanin and blood, is a complicating factor. However the effect on absorption of varying blood and melanin content is far smaller than the effect of papillary dermis thickness, and so the latter may still be measured. This can be done by obtaining two infrared photographs, each at a different wavelength. The chosen wavelengths are not important, but one should be further into the infrared (ie at longer wavelength) than the other. Suitable wavelength bands are 800-1000nm and 600-800nm, in that readily available infrared films and filters may be used. The brightness of points within the image obtained at the longer wavelength is affected to a greater extent by variations in the papillary dermis thickness. Conversely, the image obtained at shorter wavelength will be affected to a greater extent by other materials such as melanin and blood. By predicting the brightnesses of points of differing papillary dermis thickness and amounts of melanin which absorb near-infrared radiation at the two different infrared wavelengths, a reference graph (Fig 1) can be obtained which consists of lines of constant papillary dermis thickness, wherein Primary 1 is the measurement made at the longer (800-1000nm) wavelength and Primary 2 is the measurement made at the shorter (600-800nm) wavelength. The absorption of blood within these wavelengths is very small (a hundredth of its peak value for visible wavelengths at 600-800nm and even less for 800-1000nm) and to a first approximation may be ignored. The presence of dermal melanocytes does introduce a small error in the range of low values for both primaries, but this is insignificant

in practice. Thus, by comparing values obtained at these wavelengths with this graph, it is possible to ascertain the papillary dermis thickness. However it is within the scope of the present invention to measure brightness at such a long infra-red wavelength eg. 1100nm that the brightness would vary to such a negligible extent with melanin and blood content that it would effectively depend solely on the papillary dermis thickness. This would also reduce the error introduced by the presence of dermal melanocytes. In such a case only one set of brightness measurements would be required. Furthermore, a transformation can be calculated which allows an image of the skin to be created which represents how the skin would appear if it had a papillary dermis thickness of any predetermined value.

In a preferred embodiment, the reference colour coordinate range for healthy skin at the predetermined papillary dermis thickness is obtained as disclosed in the above-mentioned Technical Report as a curved surface lying within a three-dimensional colour space, with one of the bounding axes relating to the amount of melanin within the epidermis and the other relating to the amount of blood within the dermis. When an abnormal area is located, ie points do not lie on the normal colour surface, the melanin value within this area is estimated from the surrounding normal regions. This is then used with the corrected colour coordinates of the abnormal region at the same predetermined papillary dermis thickness to compute invasion depth. Instead of using LMS colour space, it is possible to use any other colour space, for example, the RGB colour space or a UV G IR colour space.

The dermis contrasts strongly in structure to that of the epidermis, being highly vascular, containing many sensory receptors and being made largely from collagen fibres to provide the essential structure of the skin. Between the epidermis and the dermis, the junction presents an extremely uneven boundary with finger-like dermal protrusions called dermal papillae projecting towards the skin surface. The dermis can be split into two further histologically distinct layers, the *papillary dermis* and the reticular dermis within which the structure of the collagen fibres differs significantly. The papillary dermis is situated directly below the epidermis and within which the collagen exists as a fine network of fibres. This is in contrast with the reticular dermis where the collagen fibres are aggregated into thick bundles which are arranged nearly parallel to the skin surface. In the case of melanocyte invasion of the papillary dermis, there is a layer containing blood, melanocytes and collagen, a layer containing either blood and collagen or melanocytes and collagen, depending upon whether melanocytes have passed the blood layer; and a layer containing just collagen. The different thicknesses of these layers, the amount of blood and the concentration of melanocytes along with the amount of melanin in the overlying epidermis affect the remitted light. This can be modelled by calculating the net effect of these three layers for the differing parameters outlined.

A mathematical model describing the optics of the skin has been described in the above mentioned Symon D'O Cotton's Technical Report, whose disclosure has been included herein by reference, and this model can be extended to predict colouration of skin containing dermal descent of melanocytes.

As can be seen from Fig 2, there are now four distinct layers within the dermis which can combine to construct a simple model, 1) a layer within the upper papillary dermis containing no melanin, 2) a layer within the upper papillary dermis containing melanin, 3) a layer within the lower papillary dermis containing melanin, 4) a layer within the lower papillary dermis containing no melanin.

It should also be noted that the condition of melanocytes existing up to the dermal-epidermal junction is facilitated by allowing the thickness of layer 1 to be zero and likewise melanocytes can exist up to the papillary-reticular dermis boundary by setting the thickness of layer 4 to be zero.

In computing a model to predict this colouration it is useful to make note of the fact that, as discussed in section 2.1 of the Technical Report, the amount of back scatter due to melanin can be considered negligible. Therefore, in the same manner that it was possible to apply the Kubelka-Munk theory to the papillary dermis (section 3.2.2 of the Technical Report), to compute the colouration of sections of papillary dermis containing blood, where the back scattering component of blood was considered negligible, it is possible to compute the colouration of sections containing melanocytes. In this situation $\varsigma(\lambda)$ (scattering coefficient) remains dependent only on wavelength whilst α (fraction of radiation absorbed per unit path length) becomes $\alpha(\lambda,\rho,\Phi)$ where Φ represents the density of dermal melanocytes within that layer. Further, following the proof given in equation (17) of the Technical Report, $\alpha\ (\lambda,\rho,\Phi)$ can be shown to be the sum of $\alpha_{iv}(\lambda)$, $\alpha_b(\lambda)$ and $\alpha_m(\lambda)$, where $\alpha_m(\lambda)$ is the absorption coefficient of melanin. From the above it is possible to

calculate R and T (diffuse radiation and transmission respectively). For simplicity of notation it is helpful to consider R_1 & T_1 where,

$$R_1(\lambda,\rho,\Phi,d_n) = R(\beta(k(\alpha(\lambda,\rho,\Phi)),s(\varsigma(\lambda))),K(k(\alpha(\lambda,\rho,\Phi)),s(\varsigma(\lambda))),d_n)$$

and

$$T_1(\lambda,\rho,\Phi,d_n) = T(\beta(k(\alpha(\lambda,\rho,\Phi)),s(\varsigma(\lambda))),K(k(\alpha(\lambda,\rho,\Phi)),s(\varsigma(\lambda))),d_n)$$

where d_n is the layer thickness.

As was shown in section 3.2.3 of the Technical Report, two-layer systems can be combined to produce the total remitted and transmitted light for the dermis resulting in equation (20) of the Technical Report.
This can be simplified using the geometric series

$$a + ar + ar^2 + ar^3 + \cdots = \frac{a}{1-r} \text{ if } -1 < r < 1$$

to

$$R_{1total}(\lambda,\rho_{ud},\rho_{ld},d_{ud},d_{ld}) = R_{1ud}(\lambda,\rho_{ud},d_{ud}) + \frac{T_{1ud}(\lambda,\rho_{ud},d_{ud})^2 R_{1ld}(\lambda,\rho_{ld},d_{ld})}{1 - R_{1ud}(\lambda,\rho_{ud},d_{ud})R_{1ld}(\lambda,\rho_{ld},d_{ld})}$$

Similarly, T_{1total} can be shown to be

$$T_{1total}(\lambda,\rho_{ud},\rho_{ld},d_{ud},d_{ld}) = \frac{T_{1ud}(\lambda,\rho_{ud},d_{ud}) * T_{1ld}(\lambda,\rho_{ld},d_{ld})}{1 - R_{1ud}(\lambda,\rho_{ud},d_{ud})R_{1ld}(\lambda,\rho_{ld},d_{ld})}$$

These equations can be extended, as is shown by Wan et al. [1981], to an n layered system resulting in values for $R_{12...n}$ and $T_{12...n}$ of

$$R_{12...n} = R_{12...n-1} + \frac{T_{12...n-1}^2 R_n}{1 - R_{12...n-1}R_n}$$

$$T_{12...n} = \frac{T_{12...n-1}T_n}{1 - R_{12...n-1}R_n}$$

This system of equations can therefore compute the total remitted and transmitted light from an n layered system of arbitrary complexity provided that the thickness and composition of the layers is specified.

For the four-layer system shown in Fig 2, this results in a value for the total light remitted and transmitted from the dermis dependent on λ, P_{ud}, P_{ld}, d_{ud}, d_{ld}, d_{l2}, Φ_{l2}, d_{l3} and Φ_{l3} where d_{l2} and d_{l3} are the thickness of layers 2 and 3 whilst Φ_{l2} and Φ_{l3} are their corresponding melanin densities. The thickness of layer 1 and layer 2 do not need to be explicitly defined as they are simply d_{ud} - d_{l2} and d_{ld} - d_{l3} respectively; similarly Φ_{l1} and Φ_{l4} are zero by definition. A further simplification is possible if it is assumed that $\Phi_{l2} = \Phi_{l3}$ leading to a single value of Φ for the dermis.

The results of these equations can be combined with the predicted light transmitted by the epidermis in the same manner as that discussed in section 3.3 of the Technical Report, thus leading to the following description of total remitted, S_{rd}, and transmitted S_{td}.

$$S_{rd}(\lambda,\rho_{ud},\rho_{ld},d_{ud},d_{ld},d_{l2},d_{l3},\Phi,d_m) = R_{2total}(\lambda,\rho_{ud},\rho_{ld},d_{ud},d_{ld},d_{l2},d_{l3},\Phi)\theta(\lambda,d_m)^2 S(\lambda)$$

$$S_{td}(\lambda,\rho_{ud},\rho_{ld},d_{ud},d_{ld},d_{l2},d_{l3},\Phi,d_m) = T_{2total}(\lambda,\rho_{ud},\rho_{ld},d_{ud},d_{ld},d_{l2},d_{l3},\Phi)\theta(\lambda,d_m)^2 S(\lambda)$$

These can be used to predict the value of the corresponding LMS primaries

$$L(\rho_{ud},\rho_{ld},d_{ud},d_{ld},d_{l2},d_{l3},\Phi,d_m) = \int_0^\infty R_{2total}(\lambda,\rho_{ud},\rho_{ld},d_{ud},d_{ld},d_{l2},d_{l3},\Phi)\theta(\lambda,d_m)^2 S(\lambda)S_L(\lambda)d\lambda$$

$$M(\rho_{ud},\rho_{ld},d_{ud},d_{ld},d_{l2},d_{l3},\Phi,d_m) = \int_0^\infty R_{2total}(\lambda,\rho_{ud},\rho_{ld},d_{ud},d_{ld},d_{l2},d_{l3},\Phi)\theta(\lambda,d_m)^2 S(\lambda)S_M(\lambda)d\lambda$$

$$S(\rho_{ud},\rho_{ld},d_{ud},d_{ld},d_{l2},d_{l3},\Phi,d_m) = \int_0^\infty R_{2total}(\lambda,\rho_{ud},\rho_{ld},d_{ud},d_{ld},d_{l2},d_{l3},\Phi)\theta(\lambda,d_m)^2 S(\lambda)S_S(\lambda)d\lambda$$

A further generalisation can be made to any primary, P_n, leading to the following equation where S_n defines the spectral response of that primary.

$$P_n(\rho_{ud}, \rho_{ld}, d_{ud}, d_{ld}, d_{l2}, d_{l3}, \Phi, d_m) = \int_0^\infty R_{2total}(\lambda, \rho_{ud}, \rho_{ld}, d_{ud}, d_{ld}, d_{l2}, d_{l3}, \Phi)\theta(\lambda, d_m)^2 S(\lambda) S_{P_n}(\lambda) d\lambda$$

This equation can then be used to generate the expected colouration of human skin exhibiting, dermal descent of melanocytes.

The result of this analysis is that it is possible for the same colouration to result from different combinations of the above parameters. This complicates the measurement of the dermal invasion of melanocytes. Indeed, to obtain this measurement, it is necessary to know the amount of melanin in the overlying *dermis*. However, at points where dermal invasion has taken place, this parameter is difficult to determine simply by comparing colour coordinates of the abnormal location with colour coordinates for healthy skin. It is for this reason that, in the present invention, abnormal regions are identified by reference to a reference colour coordinate range for healthy skin, and then the abnormal colour coordinates are compared with the colour coordinates at one or more healthy skin locations adjacent the abnormal skin location. In this way, the effect of what would have been the normal epidermal melanin level in the abnormal skin location can be taken into account, thereby enabling a more accurate determination of melanocytic descent. It is within the scope of the present invention to measure the epidermal melanin levels directly, for example using polarized light, and to incorporate such measurements in the measuring step (ii) above.

By comparing the values of the skin image represented in a certain colour space with theoretically calculated values covering all possible amounts of blood, dermal melanocyte penetration and melanocyte concentration within the same colour space, the values of those three parameters can be obtained for every point in the image. Since the papillary dermis thickness and epidermal melanin content are known, it is possible to compute a detailed three-dimensional reconstruction of the top layers of human skin. This is of great potential interest to the medical profession and enables routine examination of the internal structure of living skin just as X-rays, NMR and ultrasound are used for examining other parts of the body. It is also within the scope of the invention to acquire the infra-red and/ or visible images using lasers of different wavelengths

It is possible to use a computer programmed with the above algorithms to perform the actual calculations. However, before these calculations can be performed, an image of the area of skin under investigation must be represented in the same colour space as for the healthy skin reference colour coordinate range. This can be done in a number of ways. In one way, the skin colour coordinates are acquired from an image using the same lighting conditions and a CCD camera calibrated in the same way as that used to produce the healthy skin reference colour coordinate range. Alternatively, if exactly the same lighting conditions are not used, a white standard or other appropriate correction factor can be used to allow calibration of the image within the software. As a further alternative, a colour image can be acquired using a colour photographic film which is then digitised. This can be performed using either exactly the same lighting conditions and a calibrated set-up or again with the inclusion of a white standard or other appropriate correction factor. It is within the

scope of this invention to obtain both the infra-red and visible images a single digital camera.

The present invention will now be described in further detail and with reference to the accompanying drawings, in which:-

Fig 1 is a graph showing variation of brightness with papillary dermis thickness for primaries 1 and 2. as described hereinabove;

Fig 2 is a schematic cross-sectional view through a section of skin illustrating melanocytic descent into the *papillary dermis*;

Fig 3 is a schematic cross-sectional view through a section of skin illustrating normal, healthy regions and an abnormal region where, in this case, melanocytic descent into the *papillary dermis* and the *reticular dermis* has taken place;

Fig 4 is a block diagram showing the steps involved in one embodiment of the method of the present invention;

Fig 5 is a diagram showing the predicted surface of normal skin colouration within a three-dimensional colour space;

Fig 6 is a diagram showing colouration within the skin cancer that is shown in Fig 7 in the same 3-D colour space as depicted in Fig 5, wherein areas of healthy and unhealthy colouration are shown; and

Fig 7 is a photographic image of the skin cancer.

Referring now to Fig 3 of the drawings, a schematic skin section is shown wherein melanocytes (indicated by the black circles in Fig 3) in normal healthy skin are present in the lower part of *epidermis* 10 adjacent but above the dermo-epidermal junction 12 between the *epidermis* and the *papillary dermis* 14. The Breslow thickness referred to above is the depth of melanocyte invasion in millimetres measured from granular layer 16 which is a layer in the *epidermis* 10 where the skin goes scaly and forms the tough outer cornified layer 18. In the abnormal region of the skin, the melanocytes are shown as having descended not only into the *papillary dermis* 14, but also into the underlying *reticular dermis* 20 lying above the subcutaneous fat layer 22. It is to be appreciated that, in other cases, melanocytic decent can be into any layer of the skin and may even be into the subcutaneous fat layer 22.

Referring now to Fig 4, there is shown a block diagram illustrating the steps involved in a typical method of measurement in accordance with the present invention. In Fig 4, block 38 exemplifies method step (i) above- the determination of papillary dermis thickness by shining infrared light at two wavelengths on an area of skin being subjected to measurement and measuring the amount of light reflected from a plurality of points within that area. Block 40 exemplifies method step (ii) above- the acquisition of an image at visible wavelengths of the same skin area. This can be by CCD camera, digitised film or any other convenient means. Block 42 exemplifies method step (iii) above- the transformation of the image into corrected colour space of the skin model at a predetermined papillary dermis thickness. Block 44 exemplifies method steps (iv and v) above- the identification of abnormal regions by comparing the corrected skin

colour coordinates with the reference colour coordinate range. Block 44 exemplifies method step (vi) above- use of the corrected colour space to calculate the amounts of *epidermal* melanin within normal regions adjacent to the abnormal regions and use thereof to give an indication of the amounts thereof which would have been in the abnormal regions (corrected to the predetermined papillary dermis thickness) had they been normal. Block 48 exemplifies a first part of method step (vii) above- calculation of *dermal* invasion using the measured colouration of the abnormal regions and the calculated amount of *epidermal* melanin from 46. Block 50 exemplifies a second part of method step (vii) above- transformation of the calculated *dermal* invasion into either the Breslow thickness or the Clark's level of invasion. This can be reported as either representing the maximum invasion or as an image showing invasion over the skin.

Referring now to Fig 5, the shaded surface indicates the range of colourations which can exist in normal healthy skin corrected to the predetermined papilliary dermis thickness. Skin colourations which depart from this surface are indicative of skin abnormalities.

Referring now to Figs. 6 and 7, it can be seen that a region of the skin which is shown in Fig 7 and which is indicated by arrow H in Fig 6 lies at a position corresponding to part of the shaded surface illustrated in Fig 5 and is indicative of normal healthy skin, whereas an adjacent region indicated by arrow U in Fig 6 lies outside such surface and is indicative of abnormal unhealthy skin. Comparison of the coloration of these two adjacent regions H and U enables the depth of melanocyte invasion in the cancerous region of the skin in Fig 7 to be computed.

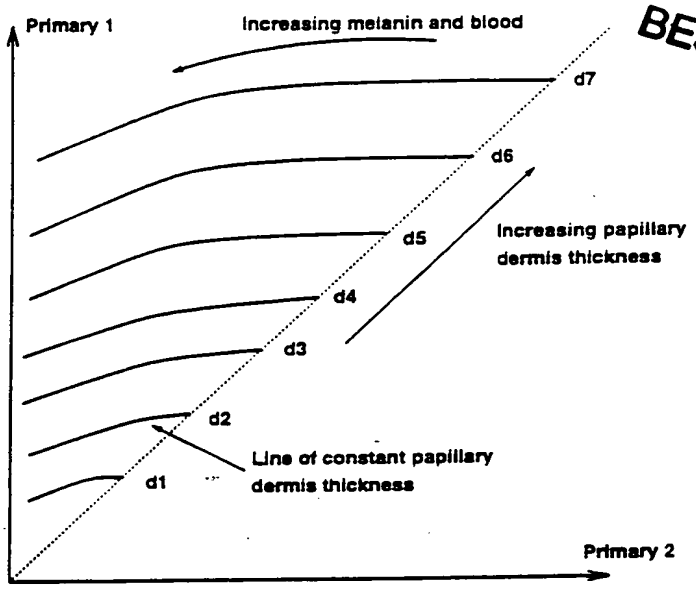


FIG 1

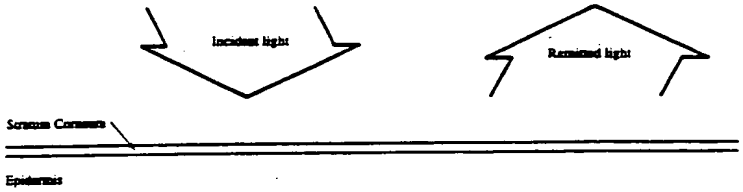
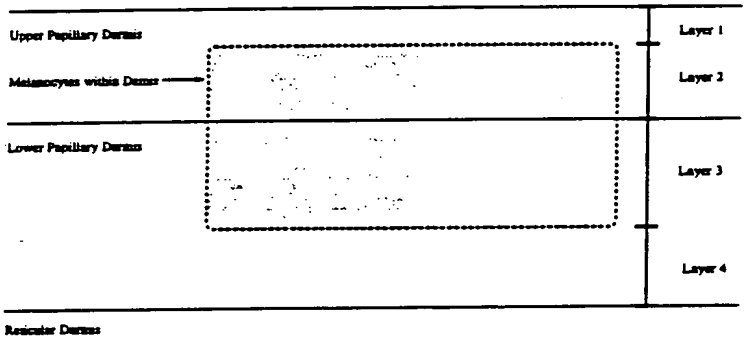


FIG 2



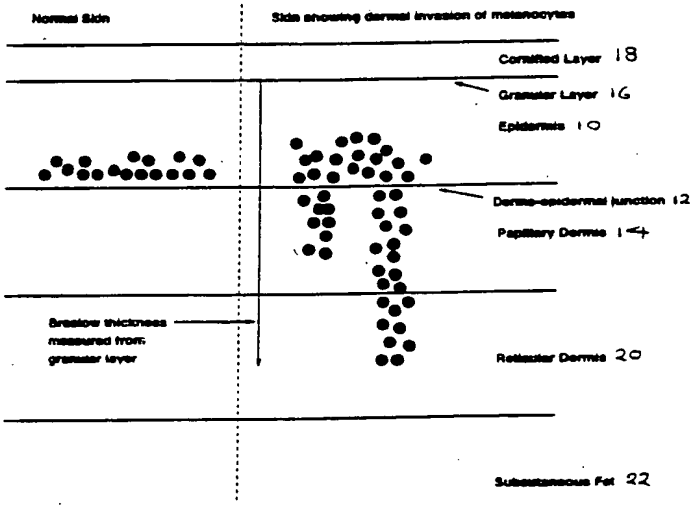


FIG 3

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Fig 4

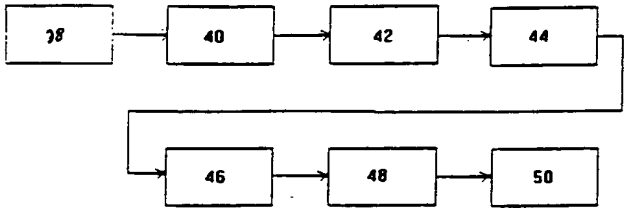

Fig 5

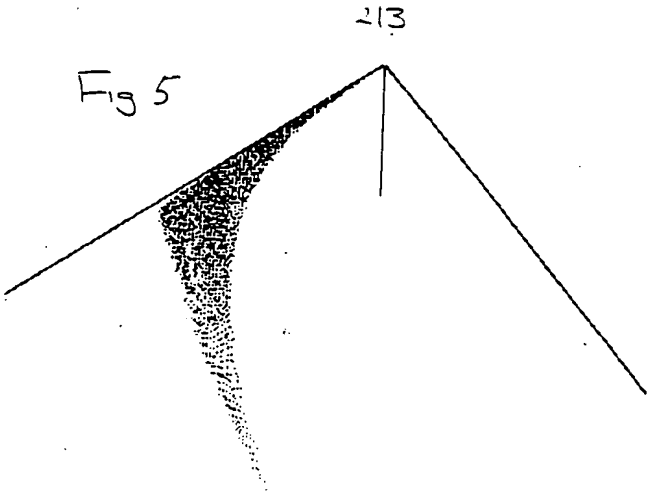

Fig. 6

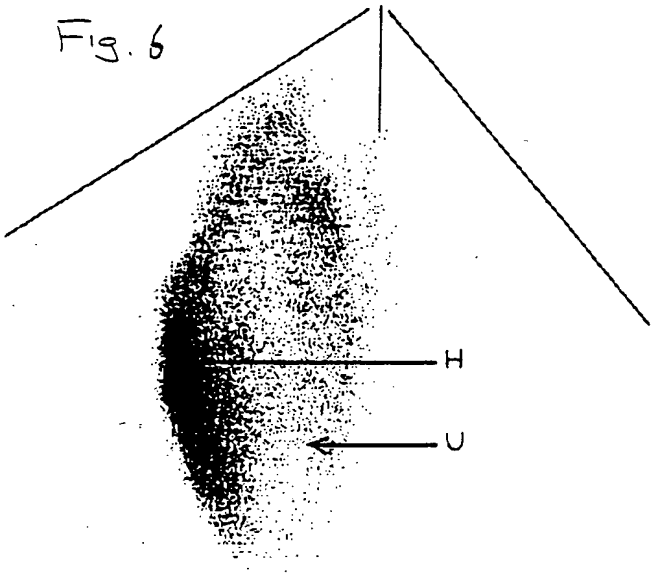

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FIG 7

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